

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-555/S-008

19-555/S-016

CORRESPONDENCE

SCHERING CORPORATION

2000 GALLOPING HILL ROAD



KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

September 28, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 18-827 / S-020 & S-022
Lotrisone Cream
NDA 19-555 / S-016
Diprolene ® AF Cream
NDA 17-536 / S-024
Diprosone ® Cream
NDA 17-691 / S-024
Diprosone ® Ointment
NDA 17-781 / S-022
Diprosone ® Lotion

SUBJECT: RESPONSE TO FDA INFORMATION REQUEST

Dear Dr. Wilkin:

Reference is made to the teleconference between Mr. Frank Cross, Ms. Olga Cintron and Schering on September 28, 2001 regarding a date for implementation of proposed packaging and labeling changes for the above mentioned products.

Based on our discussion, Schering hereby confirms that packaging and labeling changes for the above mention products will be implemented within three (3) months of receipt of FDA's approval letter.

If you have any further questions, please contact Yvette Henderson at 908-740-2179 or Mary Jane Nehring at 908-740-5713.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 33 (j) as well as the FDA regulations.

Sincerely,

Mary Jane Nehring
Senior Director, Marketed Products
Support and Training
Worldwide Regulatory Affairs

Desk Copy: Frank Cross (via fax)
Olga Cintron (via fax)

NDA SUPPL AMENDMENT
SES-016/NC

SCHERING CORPORATION

2000 GALLOPING HILL ROAD



KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

September 25, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 18-827 / S-020 & S-022

Lotrisone Cream

NDA 19-555 / S-016

Diprolene ® AF Cream

NDA 17-536 / S-024

Diprosone ® Cream

NDA 17-691 / S-024

Diprosone ® Ointment

NDA 17-781 / S-022

Diprosone ® Lotion

RECEIVED

SEP 27 2001

MEGA/CDER

SUBJECT: RESPONSE TO FDA INFORMATION REQUEST

Dear Dr. Wilkin:

Reference is made to the teleconference between Mr. Frank Cross, Ms. Olga Cintron and Schering on September 25, 2001 regarding a timeframe for implementation of proposed packaging and labeling changes for the above mentioned products.

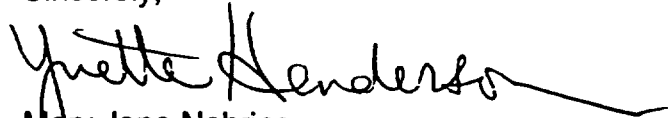
Based on review of our current inventory and estimated timeframe required to revise artwork for all product labeling, Schering will implement packaging and labeling changes within six (6) months of receipt of FDA's action letter.

If you have any further questions, please contact Yvette Henderson at 908-740-2179 or Mary Jane Nehring at 908-740-5713.

ORIGINAL

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 33 (j) as well as the FDA regulations.

Sincerely,

A handwritten signature in black ink, appearing to read "Yvette Henderson", with a long horizontal flourish extending to the right.

Mary Jane Nehring
Senior Director, Marketed Products
Support and Training
Worldwide Regulatory Affairs

Desk Copy: Frank Cross (via fax)
Olga Cintron (via fax)

NDA SUPPL AMENDMENT

SCHERING CORPORATION

2000 GALLOPING HILL ROAD



KENILWORTH, N.J. 07033

RECEIVED
SEP 26 2001
MEGA/CDER
TELEPHONE: (908) 298-4000

September 25, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 19-555 / S-016 ✓
Diprolene ® AF Cream
NDA 17-536 / S-024
Diprosone ® Cream
NDA 17-691 / S-024
Diprosone ® Ointment
NDA 17-781 / S-022
Diprosone ® Lotion

SUBJECT: DRAFT LABELING RESPONSE

Dear Dr. Wilkin:

Reference is made to our October 4, 2000 pediatric efficacy supplement, our May 31, 2001 Amendment to the pediatric efficacy supplement, the Agency's August 1, 2001 faxes of revised draft labeling for the betamethasone products and the September 20, 2001 teleconference between Schering and the Agency.

We have reviewed the Agency's proposed wording and accept all revisions with the exception of one section.

In the **INDICATIONS AND USAGE** section of all four package inserts:

Schering proposes the following statement:

"Diprosone Cream, Ointment or Lotion (Diprolene AF Cream) is a medium (high) potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years and older."

ORIGINAL

In place of:

"Diprosone Cream, Ointment or Lotion (Diprolene AF Cream) is a medium (high) potency corticosteroid indicated in patients 13 years and older for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses."

If you have any further questions, please contact Todd Paporello, Pharm.D. at 908-740-4252 or Mary Jane Boyle at 908-740-5693.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 33 (j) as well as the FDA regulations.

Sincerely,

A handwritten signature in black ink, appearing to read "Joseph F. Lamendola".

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Copies:
Olga Cintron (Fax)

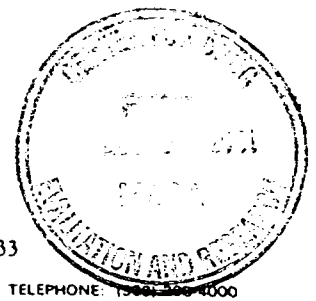
TP/es

NDA SUPPL AMENDMENT
SES-022/BL
SCHERING CORPORATION

2000 GALLOPING HILL ROAD



KENILWORTH, N.J. 07033



TELEPHONE: 1-800-526-4000

August 2, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

**NDA 19-555/S-016
DIPROLENE AF Cream
NDA 17-536/S-024
DIPROSONE Cream
NDA 17-691/S-024
DIPROSONE Ointment
NDA 17-781/S-022
DIPROSONE Lotion**

SUBJECT: RESPONSE TO FDA REQUEST

Dear Dr. Wilkin:

Reference is made to the telephone calls from Olga Citron on June 16 and August 1, 2001 in which she requested that product labeling be submitted for the supplemental applications submitted by Schering for Diprolene AF Cream, Diprosone Cream, Diprosone Lotion and Diprosone Ointment.

In response to Ms. Cintron's request, enclosed are cartons and labels for Diprolene AF Cream, Diprosone Cream, Diprosone Lotion and Diprosone Ointment.

If additional information is needed, please call Ms. Yvette Henderson at (908) 740-2179.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Mary Jane Nehring
Senior Director, Marketed Products
Support and Training
Worldwide Regulatory Affairs

Desk Copy: Frank Cross

YH/es: Attachment

ORIGINAL

SCHERING CORPORATION

2000 GALLOPING HILL ROAD



KENILWORTH, N.J. 07033

TELEPHONE: (908) 736-4000



June 18, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 19-555 / S-016
DIPROLENE® AF
(betamethsone
dipropionate) Cream
0.05%

SUBJECT: AMENDMENT TO SUPPLEMENT S-016
RESUBMISSION OF ELECTRONIC FILES

Dear Dr. Wilkin:

Reference is made to the amendment to Diprolene AF Cream Supplement NDA 19-555/S-016 submitted on May 31, 2001.

Reference also is made to a teleconference on June 12, 2001 with Randy Levin (Electronic Submission Coordinator) in which he requested another disk with copies of the letter, FDA Form 356H and SAS datasets with the dictionary of terms and annotated case report forms. PDF and WORD files of the draft labeling and the case report form for the subject with a serious adverse event were also requested to be included on the disk.

In response to his request, a revised CD-ROM disk is being submitted to the Electronic Submission Coordinator. The following items are being included on the disk:

- A copy of this letter. A copy of the May 31, 2001 letter submitted with amendment to NDA 19-555/S-016 is provided in Attachment 1. (PDF Format)
- FDA Form 356H (PDF Format)
- Abbreviated SAS datasets for each study (P01262, P01261, P01263 and P01260. Abnormal cortisol values have been flagged as discussed on April 25, 2001 between Ms. Krhoun (Schering-Plough) and Ms. Cintron (FDA). Please note that the electronic folders labeled by the NDA number have been

DUPLICATE

changed to designate each study dataset. The only NDA reference included is N19555, which is the NDA to which the report was submitted. (SAS Format)

- Dictionary of terms (PDF Format)
- Annotated case report forms for each study (P01262, P01261, P01263 and P01260). (PDF Format)
- PDF and WORD files of the draft labeling and annotated draft labeling
- Serious Adverse Event Case Report Form (PDF Format)

If you have any questions regarding this submission, please feel free to contact Elin Krhoun at (908) 740-5434 or Mary Jane Boyle at (908) 740-5693.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 33 (j) as well as the FDA regulations.

Sincerely,



Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Copies:

Randy Levin: Letter
(via fax)

Electronic Submissions Coordinator: CD-ROM

EK/es: Attachment

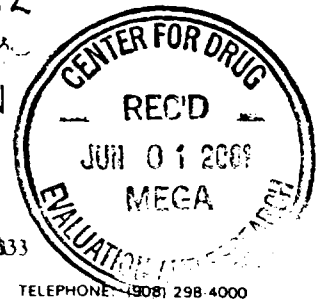
SES-016/BZ

SCHERING CORPORATION

2000 GALLOPING HILL ROAD



KENILWORTH, N.J. 07033



May 31, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 19-555 / S-016
DIPROLENE® AF
(betamethasone
dipropionate) Cream
0.05%

**SUBJECT: FINAL SUBMISSION OF PEDIATRIC STUDY REPORTS;
AMENDMENT TO SUPPLEMENT S-016**

Dear Dr. Wilkin:

Enclosed is an amendment to the pending DIPROLENE® AF Cream, 0.05% pediatric supplement NDA 19-555 / S-016. The supplement was submitted on October 4, 2000, in response to the July 16, 1999 official written request and the April 19, 2000 amended request for betamethasone dipropionate products and LOTRISONE® (clotrimazole and betamethasone dipropionate) Cream, 0.05%. Reference is also made to the meeting on March 19, 2001 that was held in response to the December 21, 2000 letter regarding the DIPROLENE® AF and DIPROSONE® pediatric supplements.

Included in this amendment:

- The final study report with re-analysis according to Cortrosyn® labeling and the ICH guidelines for age group distribution for the four betamethasone dipropionate safety studies in pediatric subjects with atopic dermatitis. These safety studies include: DIPROLENE® AF (augmented betamethasone dipropionate) Cream, 0.05%, (Protocol P01260); DIPROSONE® (betamethasone dipropionate) Ointment, 0.05%, (Protocol P01261); DIPROSONE® (betamethasone dipropionate) Cream, 0.05%, (Protocol P01262); and DIPROSONE® (betamethasone dipropionate) Lotion, 0.05%, (Protocol P01263)

ORIGINAL

- Abbreviated SAS data sets flagged for abnormal cortisol values with supporting information as discussed on April 25, 2001 between Ms. Krhoun (Schering-Plough) and Ms. Cintron (FDA). The following information is being provided:
 - Files for each study which are designated as follows: (Submitted to the Electronic Submissions Coordinator)
 - No. 17-536 for P01262
 - No. 17-691 for P01261
 - No. 17-781 for P01263
 - No. 19-555 for P01260
 - Dictionary of Terms
 - Annotated Case Report Forms for each study
- A Microsoft WORD® format of the final study report text
- Revised, annotated labeling (hard copy and electronic Microsoft WORD® format) that includes the updated study data from the final report. This version supercedes the labeling sent on October 4, 2000. The following sections of the DIPROLENE® AF Cream, 0.05%, labeling have been modified (Please refer to the highlighted sections):
 - CLINICAL PHARMACOLOGY
 - Pharmacokinetics
 - INDICATIONS AND USAGE
 - PRECAUTIONS
 - Information for Patients
 - Pediatric Use
 - ADVERSE REACTIONS
 - DOSAGE AND ADMINISTRATION

The product labeling for the sections, CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: Pediatric Use, included in this submission used the study protocol criteria (i.e., adrenal suppression was indicated by either a ≤ 4.5 mcg/dL pre-stimulation cortisol, or a cosyntropin post-stimulation cortisol ≤ 18 mcg/dL and an increase of ≤ 7 mcg/dL from the baseline cortisol) to describe the number of patients experiencing adrenal suppression during the clinical studies.

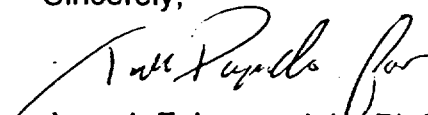
- Response to Reviewer's comments dated March 20, 2001 including Environmental Assessment for Categorical Exclusion
- Spontaneous Adverse Event Reports
- Literature Search
- Serious Adverse Event Case Report Form (CD-ROM)

Schering Corporation certifies that a copy of the cover letter and technical section of this amendment is being sent to FDA's San Juan, Puerto Rico District Office and to the New Jersey District Office.

If you have any questions regarding this submission, please feel free to contact Todd Paporello, Pharm.D. at (908) 740-4252 or Mary Jane Boyle at (908) 740-5693.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 33 (j) as well as the FDA regulations.

Sincerely,



Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Copies:

Electronic Submissions Coordinator: CD-ROM with SAS data sets
Kevin White (for Olga Cintron): DESK COPY: Volume 1 and WORD disks

TP:es

Enclosure

SCHERING CORPORATION

2000 GALLOPING HILL ROAD



KENILWORTH, N.J. 07033



October 4, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room (HFD-540)
5600 Fishers Lane
Rockville, MD 20857
Attention: Jonathan Wilkin, M.D., Director

**DIPROLENE® AF (betamethasone
dipropionate)
Cream**

NDA 19-555

NDA NO 19-555 RFA NO 016
NDA SUPPL FOR SEP
NDA SUPPL FOR SEP-016/pm

Division of Dermatologic and Dental Drug Products

**SUBJECT: SUBMISSION OF PEDIATRIC STUDY REPORTS -
PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED
LABELING SUPPLEMENT**

Dear Dr. Wilkin:

Enclosed is a labeling supplement to approved NDA 19-555, DIPROLENE® (augmented betamethasone dipropionate cream) Cream, 0.05%, in response to an official Written Request for pediatric studies dated July 16, 1999 amended April 19, 2000 for betamethasone dipropionate products and LOTRISONE® (clotrimazole and betamethasone dipropionate cream) Cream. Reference is made to the teleconference on September 15, 2000 that was held to discuss difficulties in enrollment of tinea cruris patients ages 12 to 16 years and broadening of the evaluable atopic dermatitis subgroup patients ages 6 to 8 years. A request for further amendments to the Pediatric Request was submitted on September 28, 2000. (ENCLOSURE 1)

As discussed with Ms. Fornaro, included in this supplement is a combined study report for the four betamethasone dipropionate safety studies in pediatric subjects ages 3 months to 12 years with atopic dermatitis with DIPROLENE® AF (augmented betamethasone dipropionate cream) Cream, 0.05%, (Protocol P01260); DIPROSONE® (betamethasone dipropionate cream) Cream, 0.05%, (Protocol P01262); DIPROSONE® (betamethasone dipropionate ointment) Ointment, 0.05%, (Protocol P01261); and DIPROSONE® (betamethasone dipropionate lotion) Lotion, 0.05% (Protocol P01263). Safety studies were also conducted with LOTRISONE® (clotrimazole and betamethasone dipropionate cream) Cream in patients 12 to 16 years of age with tinea cruris or tinea pedis. Results of these studies also are being submitted to NDA 18-827 this same day, October 4, 2000.

The four atopic dermatitis safety studies in pediatric subjects were each terminated due to HPA effects as described in the "Rate-Limiting" safety, "Deviation (reduction of 10% or greater) from the lower normal limit for plasma (serum) cortisol and/or the Cosyntropin® (ACTH) challenge response in 10% of subjects (Amendment to the Pediatric Request dated April 19, 2000). Therefore, enrollment of 50 evaluable subjects ages 3 months to 12 years with 30 evaluable subjects ages 6-8 years was not achieved. The Agency was notified of the termination of these studies:

- DIPROSONE® Lotion Study P01263: [REDACTED] on April 21, 2000 due to "Rate-Limiting" safety in the 8 to 12 year and 6 to 8 year age groups.
- DIPROSONE® Cream Study P01262: [REDACTED] on July 14, 2000 due to "Rate-Limiting" safety in the 6 to 8 and 2 to 5 year age groups.
- DIPROSONE® Ointment Study P01261: [REDACTED] on September 26, 2000 due to "Rate-Limiting" safety in the 6 to 8 age group.
- DIPROLENE® AF Cream Study P01260: [REDACTED] on September 26, 2000 due to "Rate-Limiting" safety in the 2 to 6 year age group.

Based on the available safety data from **Study P01260** submitted in this supplement, the following sections of the DIPROLENE® AF Cream, 0.05%, labeling have been modified:

CLINICAL PHARMACOLOGY:

Pharmacokinetics:

INDICATION AND USAGE:

PRECAUTIONS:

Information for Patients:

Pediatric Use:

ADVERSE REACTIONS:

Betamethasone dipropionate products and LOTRISONE® (clotrimazole and betamethasone dipropionate cream) Cream were included in the Food and Drug Administration's list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population and appeared in the Federal Register Docket No. 98N-0056. Therefore, labeling supplements dated October 4, 2000 are also being submitted for the following products in fulfillment of this Written Request:

NDA 17-536 DIPROSONE® Cream
NDA 17-691 DIPROSONE® Ointment
NDA 17-781 DIPROSONE® Lotion
NDA 18-827 LOTRISONE® Cream

The reports for betamethasone dipropionate products and Lotrisone Cream submitted on October 4, 2000 contain 2-week, post-treatment follow-up data. Final

reports with 4-week, post-treatment follow-up data will be submitted in full labeling supplements pursuant to the Amended Pediatric Request dated April 19, 2000.

We believe that we have met all the requirements in the Written Request and amended Written Request with the exception of the required 45 tinea cruris subjects treated with LOTRISONE Cream. However, we have requested a revision to the Written Request on September 28, 2000 due to the limited availability of patients 12 to 16 years of age with tinea cruris. **(ENCLOSURE 1)** All studies referenced herein are responsive to the Written Request, Amendments and Requested Amendments and were conducted in accordance with commonly accepted scientific principles.

In accordance with the Agency's guidance,^a we are requesting a pediatric exclusivity determination based on the studies included in this submission, and the studies and labeling supplements submitted to the other NDA's as cited above.

The revisions requested to Diprolene Gel, Diprolene Ointment and Diprolene Lotion labeling have been implemented. Copies of this labeling is provided in Section 20, Other Information.

These supplements have been prepared in accordance with 21 CFR 314.50, 314.70 and 201.57. The following guidances were also used in preparation of this supplement: "The Content and Format for Pediatric Use Supplements" and "Qualifying for Pediatric Exclusivity Under Section of the Federal Food, Drug and Cosmetic Act". A Table is attached with identifies the kind of pediatric data submitted **(ENCLOSURE 2)**. The study reports were prepared in a format consistent with FDA's "Guidelines for Format and Content of Clinical and Statistical Sections of New Drug Applications (July 1988)" and "ICH:E3: Structure and Content of Clinical Study Reports (July 1996)"

References to the requested data and information in the official Pediatric Written Request has been included in Volume 1, Section 20 of this submission. In addition, a faxed copy of this letter and those for the other supplements was sent, at time of this mailing, to the OFFICE OF GENERIC DRUGS (OGD), Attn: Director, OGD (HFD-600), 301-594-0183.

Pursuant to 21 USC 379(h)(a)(1)(F), no fee is due upon submission of this supplement since it only includes new pediatric safety information to an approved product.

^aGuidance for Industry, Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act, September 1999

SCHERING CORPORATION

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SEB-016(BM)

2000 GALLOPING HILL ROAD



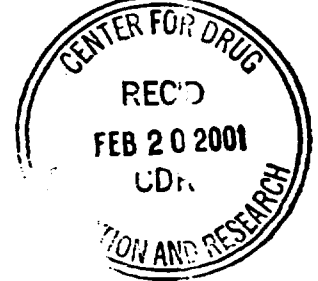
KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

February 16, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 19-555
Diprolene AF Cream



SUBJECT: RESPONSE TO FDA REQUEST

Dear Dr. Wilkin,

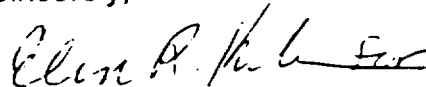
Reference is made to the January 3, 2001 fax regarding our October 4, 2000 pediatric studies for Diprolene AF Cream, Diprosone Ointment Diprosone Cream, and Diprosone Lotion. The interim study report and safety update for these studies was included in NDA 19-555/S-016.

Reference is also made to the January 31, 2001 teleconference with Dr. Cook and Ms. Wright in which clarification of the comments was requested, in particular for the second question regarding follow-up information for subjects who had Cortrosyn stimulation of less than 18 mcg/dL serum cortisol. Dr. Cook also asked that an explanation why subjects with Cortrosyn <18 mcg/dL were being allowed into the study.

We are providing responses to these comments.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

A handwritten signature in dark ink, appearing to read "Joseph F. Lamendola".

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

EK/es
Attachment